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(54) HYDROHALOGENATION OF MYRCENE AND HYDROXY AND ESTER DERIVATIVES OF THE PRODUCTS

(71) We, BUSH BOAKE ALLEN LIMITED, a British Company of 20/42 Wharf Road, London N.1, do hereby declare the invention, for which we pray that a Patent may be granted to us and the method by which it is to be performed to be particularly described in and by the following statement:—

This invention relates to the hydrohalogenation of myrcene (2-methyl-6-methylene-2,7-octadiene).

It is known that myrcene may be reacted with hydrogen chloride or hydrogen bromide to provide a variety of products depending on the reaction conditions employed. Reaction of myrcene with one mole of hydrogen chloride or bromide generally leads to a mixture of myrcenyl halide (2-halo-2-methyl-6-methylene-7-octene) resulting from addition to the isolated ethylenic bond; linalyl halide (6-halo-2,6-dimethyl-2,7-octadiene) resulting from 1,2 addition to the conjugated double bond system; and geranyl (neryl) halides (8-halo-2,6-dimethyl-2,6-octadiene) resulting from 1,4 addition to the conjugated double bond system. α -Terpinyl halide is also formed as the result of side reactions. It is now customary to influence the direction of the reaction by the action of various catalysts notably copper salts. A number of sets of reaction conditions have been proposed and prior art in this regard is conveniently summarised in Specification No. 1,072,701. Generally it has been desired to produce the geranyl(neryl) and/or linalyl halides and the efforts of previous workers in this field have generally been directed to maximising the yield of these compounds by the use of appropriate catalysts and/or temperature conditions. Thus Specification No. 1,072,701 advocates the reaction of myrcene with hydrogen bromide at 60°C to 120°C to give

a good yield of neryl, geranyl and linalyl bromides.

More recently in Specification No. 1,141,140 it has been advocated to carry out the monohydrohalogenation of myrcene in the presence of a Lewis acid and/or a high surface area material as catalyst to obtain an improved yield of the myrcenyl chloride. The reaction temperature is stated to be advantageously from -20°C to +50°C, preferably at 0-20°C. It is also stated therein that under these conditions of temperature and presence of catalyst there can be isolated from the reaction mixture after hydrolysis the novel alcohol, 3,3-dimethyl-1-vinylcyclohexanol. However no further details are given and it can therefore be assumed that the compound was isolated as a by-product and in a low yield.

We have now discovered that 3,3-dimethyl-1-vinylcyclohexanol and its allylic isomer, 1-(2'-hydroxy)ethylidene-3,3-dimethylcyclohexane which have the respective formulae I and II, below, where X is hydroxyl, can surprisingly be obtained in very satisfactory yield if myrcene is mono-hydrohalogenated at lower temperatures than hitherto advocated, i.e. at from -25°C to -80°C, and preferably in the absence of a catalyst. The relative proportion of the tertiary alcohol (I), and the primary alcohol isomer (II), can be varied according to the method used for the isolation of the alcohol from the reaction mixture obtained after mono-hydrohalogenation. The two alcohols (I and II) and their esters find use in perfumery compositions. These alcohols have also previously been prepared by Vodoz and Schinz [Helv. Chem. Acta 33, 1321-4 (1950)] but these workers used an entirely different synthetic route.

Accordingly, the invention provides a pro-

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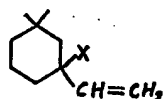
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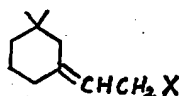
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cess for the production of compounds of the formula:



I

and/or compounds of the formula:



II

where X is a chlorine or bromine radical, a hydroxyl group or a group of formula —OCOR where RCOOH is a carboxylic acid, which comprises reacting myrcene with up to 1.2 molar proportions of hydrogen chloride or hydrogen bromide at a temperature of from -25°C to -80°C and optionally subsequently hydrolysing or acylating the reaction product.

The derivatives obtained may be chloride or bromide being 3,3 - dimethyl - 1 - vinyl - cyclohexyl halides and/or 1 - (2' - halo) - ethylidene - 3,3 - dimethylcyclohexanes, or they may be the corresponding alcohols of the formulae I and II above or they may be carboxylate esters of these alcohols. Such derivatives may be obtained by several variations of the process of the invention. For example the initially formed halides I and II ($\text{X}=\text{Cl}$ or Br) may be directly hydrolysed, either before or after separation and/or purification, to obtain the alcohols of formulae I and II ($\text{X}=\text{OH}$), or they may be reacted with a metal carboxylate salt to form acylates of alcohols of formulae I and II and these acylates, in turn, may be saponified to produce the alcohols (I) and (II) ($\text{X}=\text{OH}$). Since the compounds (I) and (II) are allylic isomers there is a tendency for the various derivatives to be interconverted during the various transformations, as more fully described hereafter.

The process of the invention is preferably carried out using 0.8—1.1 molar proportions of hydrogen halide per mole of myrcene; most preferably substantially equimolar proportions of the reactants are employed. Hydrogen chloride is preferred over hydrogen bromide. The reaction is preferably uncatalysed and, accordingly, the reaction mixture should preferably be substantially free from

copper and its compounds and also free from radical-forming initiators and not be exposed unduly to ultra-violet light. The reaction temperature should be from -25°C to -80°C and a temperature of -50°C to -70°C especially -60°C to -70°C , is preferred. The reaction is best carried out under substantially anhydrous conditions. If desired, an inert solvent, such as light petroleum or an ether, may be present, but this is usually unnecessary. The progress of the reaction may be followed by monitoring the weight increase of the reaction mixture and, if desired, it may be controlled by suitable monitoring devices, e.g. by periodic or continuous spectroscopic examination or by gas-liquid chromatography.

When approximately one molecular proportion of the hydrogen halide has been absorbed the reaction mixture may be subjected to fractional distillation to separation out the desired 3,3 - dimethyl - 1 - vinyl - 1 - cyclohexyl halide and 1 - (2' - halo ethyl) - idene - 3,3 - dimethylcyclohexane and these may, if desired, be further purified by repeated fractional distillation, usually under vacuum.

It is not necessary to use purified myrcene as the starting material. Equally satisfactory is crude myrcene, obtained by pyrolysis of B-pinene, with a myrcene content usually in the range 60 to 80%, the balance being mainly limonene and small amounts of α - and B-pinene.

It is preferred to convert the halide reaction product directly into other derivatives, using appropriate techniques to maximise the yield of the primary derivative (II) or tertiary derivative (I) as appropriate. Thus, for example, direct hydrolysis of the halide reaction product using an aqueous, alcoholic or aqueous/alcoholic base yields predominantly the tertiary alcohol I ($\text{X}=\text{OH}$) and this hydrolysis may be catalysed, if desired, by the presence of up to 5% by weight on the reaction mixture of copper or a compound thereof, especially with cuprous chloride. The resulting alcohol is separated and purified by fractional distillation, preferably under vacuum.

Alternatively, the halides may be converted into esters by reaction with a metal carboxylate salt, e.g. with sodium acetate. The reaction mixture should desirably be kept non-acidic to minimise elimination reactions. An uncatalysed reaction or one catalysed with copper or a copper compound, such as cuprous chloride, results in predominant formation of the tertiary ester (I, $\text{X}=\text{OCOR}$); whereas reaction in the presence of a stoichiometric quantity of a nitrogen base catalyst, such as a tertiary amine e.g. triethylamine, and in the absence of copper or copper salts yields predominantly the primary ester (II, $\text{X}=\text{OCOR}$). This is an

example of the general reaction of an allylic terpenic chloride or bromide containing 10 carbon atoms with a carboxylic acid salt in the presence of a nitrogen base catalyst and such general reaction is the subject of British Patent No. 979,523. If both a nitrogen base catalyst and cuprous chloride or bromide are present then again the formation of the tertiary ester (I) is favoured, this being an example of the general reaction of C_{10} -allylic terpenic halides with carboxylate salts in the presence of a nitrogen base and a cuprous chloride and/or bromide as claimed in British Patent No. 979,524.

The esters may be saponified, by the action of dilute alkali, to produce the alcohols and if this saponification is carried out under non-forcing conditions further allylic transformations at this stage can be minimised so that the alcohols corresponding to the esters can be obtained. Thus to obtain the primary alcohol II ($X=OH$), it is preferred first to make an ester (II $X=OCOR$), usually the acetate, followed by saponification, whereas direct hydrolysis of the myrcene monohydrohalide product is preferred where the tertiary alcohol (I, $X=OH$) is desired.

The alcohols I and II ($X=OH$) find use in perfumery as also do their esters ($X=OCOR$). For this purpose X may be the residue of any carboxylic acid, e.g. formic, acetic, propionic, caproic, benzoic, cinnamic or salicylic acid. However, preferably the ester is one of a lower monocarboxylic acid, that is one having from 1 to 5 carbon atoms, particularly formic, acetic or propionic acid. All these esters of formulae I and II ($X=OCOR$ where RCO_2H is a carboxylic acid) are novel compounds and constitute a further aspect of the present invention.

The invention is illustrated by the following Examples:—

Example 1

Dry hydrogen chloride gas was bubbled through commercial myrcene of 80% purity at -65°C until approximately 1 molecular proportion had been absorbed. The crude chlorides were acetylated using 1.25 molecular proportions of sodium acetate in the presence of 2% of triethylamine, the reaction being conducted at 90°C for 5 hours. The resulting acetate esters were saponified at 140°C with an equimolecular proportion of 46% sodium hydroxide solution to yield, after purification by fractional distillation, 1-(2'-hydroxy) ethylidene-3,3-dimethyl cyclohexane in about 50% overall yield.

Example 2

Example I was repeated but with hydrochlorination being carried out at -40°C . The alcohol II ($X=OH$) was obtained in about 30% yield.

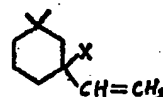
Example 3

Myrcene was hydrochlorinated at -65°C as in Example I. The resulting products were fractionated under high vacuum and there was obtained a mixture consisting of 70–80% of 1-(2'-chloro)-ethylidene-3,3-dimethylcyclohexane (I, $X=C$) and 20–30% of a-terpinyl chloride.

The mixture of crude chlorides thus obtained was hydrolysed with water and sodium bicarbonate using acetone as a solvent and containing about 10% by weight of cuprous chloride as a catalyst. This reaction mixture was stirred at -5°C for about 10 minutes and then at 0°C until no further carbon dioxide was evolved, followed by warming the reaction mixture to 40°C . Distillation of the reaction mixture under vacuum yielded 3,3-dimethyl-1-vinyl-cyclohexanol (I, $X=OH$) in an overall yield of about 60% yield.

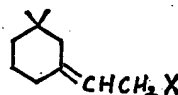
WHAT WE CLAIM IS:

1. A process for the production of compounds of the formula:



I

and/or compounds of the formula:



II

where X is a chlorine or bromine radical, a hydroxyl group or a group of formula $-OCOR$ where $RCOOH$ is a carboxylic acid, which comprises reacting myrcene with up to 1.2 molar proportions of hydrogen chloride or hydrogen bromide at a temperature of from -25°C to -80°C and optionally subsequently hydrolysing or acylating the reaction product.

2. A process according to claim 1 wherein the hydrohalogenation of myrcene is uncatalysed.

3. A process according to claim 2 wherein the hydrohalogenation of myrcene proceeds substantially in the absence of copper and its compounds and of free radical-forming initiators and is not exposed unduly to ultra-violet light.

4. A process according to any of the pre-

ceding claims wherein the hydrohalogenation of myrcene is conducted at from -50°C to -70°C .

5 5. A process according to any of the preceding claims wherein the hydrohalogenation of myrcene is conducted using from 0.8 to 1.1 molar proportions of hydrogen halide per mole of myrcene.

10 6. A process according to any of the preceding claims wherein the initially formed reaction product of the hydrohalogenation of myrcene is hydrolysed with base and subsequently purified to yield a product comprising predominantly an alcohol of the aforesaid formula I.

15 7. A process according to claim 6 wherein the basic hydrolysis step is catalysed by the presence of up to 5% by weight on the reaction mixture of copper or a compound thereof.

20 8. A process according to any of claims 1 to 5 wherein the initially formed reaction product of the hydrohalogenation of myrcene is treated with a metal carboxylate salt to yield a product comprising predominantly carboxylate ester(s) of the aforesaid formula(e) I and/or II.

25 9. A process according to claim 8 wherein the treatment with metal carboxylate salt takes place either in the virtual absence of a catalyst or in the presence of copper or a copper compound and the subsequently recovered product comprises a major proportion of a tertiary ester of the aforesaid formula I.

30 10. A process according to claim 8 wherein the treatment with metal carboxylate salt takes place in the presence of a stoichiometric quantity of a nitrogen base catalyst

and in the substantial absence of copper or copper salts and the subsequently recovered product comprises a major proportion of a primary ester of the aforesaid formula II.

40 11. A process according to any of claims 8 to 10 wherein the metal carboxylate salt is a salt of a lower monocarboxylic acid having from 1 to 5 carbon atoms.

50 12. A process according to claim II wherein the monocarboxylic acid is formic, acetic or propionic acid.

13. A process according to any of claims 1 to 5 wherein the initially formed reaction product of the hydrohalogenation of myrcene is purified to yield a product comprising a major proportion of halide(s) of the aforesaid formula(e) I and/or II.

55 14. Esters of the aforesaid formulae I and/or II wherein X is a group of the formula $-\text{OCOR}$, R being the residue of a carboxylic acid RCO_2H .

60 15. Esters according to claim 14 wherein R is an alkyl group having from 1 to 4 carbon atoms.

65 16. A process for the production of a compound/or compounds of the aforesaid formula(e) I and/or II substantially as described with reference to any of the Examples herein.

70 17. Compounds of the aforesaid formula I or II wherever prepared by a process according to any of claims 1 to 13 or 16.

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